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CASE REPORT

Seventeen Alpha-hydroxylase Deficiency

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Seventeen α-hydroxylase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia in which defects in the biosynthesis of cortisol and sex steroid result in mineralocorticoid excess, hypokalemic hypertension and sexual abnormalities such as pseudohermaphroditism in males, and sexual infantilism in females. The disease is inherited in an autosomal recessive pattern, and is caused by mutations in the gene encoding cytochrome P450c17 (CYP17), which is the single polypeptide that mediates both 17α-hydroxylase and 17,20-lyase activities. We report the case of a 15-year-old patient with 17OHD who had a female phenotype but male karyotype (46,XY). The diagnosis was made based on classical clinical features, biochemical data and molecular genetic study. Two mutations were identified by polymerase chain reaction amplification and sequencing, including a S106P point mutation in exon 2 and a 9-bp (GACTCTTTC) deletion from nucleotide position 1519 in exon 8 of CYP17. The first of these mutations was found in the father and the second in the mother, and both have been previously reported in Asia. The patient's hypertension and hypokalemia resolved after glucocorticoid replacement and treatment with potassium-sparing diuretics. Sex hormone replacement was prescribed for induction of sexual development and reduction of the final height. Prophylactic gonadectomy was scheduled. In summary, 17OHD should be suspected in patients with hypokalemic hypertension and lack of secondary sexual development so that appropriate therapy can be implemented. [*J Formos Med Assoc* 2006;105(2):177–181]

Key Words: 17α-hydroxylase deficiency, congenital adrenal hyperplasia, hypertension, hypokalemia

Seventeen α-hydroxylase deficiency (17OHD) is a rare autosomal recessive disorder with an estimated incidence of approximately 1 in 50,000 individuals.[1] It was initially described in 1966 by Biglieri et al in a genotypical female, whose condition was characterized by hypertension, hypokalemia and lack of puberty.[2] In 1970, New reported an affected genotypical male presenting with male pseudohermaphroditism.[3] The disease affects both adrenal and gonadal glands.[4] Genetic mutations have been demonstrated in the gene encoding cytochrome P450c17 (CYP17) on chromosome 10q24-q25, causing 17α-hydroxylase/17,20-lyase deficiency.[5,6] The consequent defects in the synthesis of cortisol and compensatory hypersecretion of adrenocorticotropic hormone (ACTH) stimulate the synthesis of a large quantity of 11-deoxycorticosterone (DOC) and corticosterone by the zona fasciculata. High concentrations of DOC, which is a potent mineralocorticoid, lead to hypertension, hypokalemia, a suppressed renin-angiotensin system, and low plasma aldosterone concentration. However, normal or high aldosterone levels have been reported in several cases. In gonads, the absence of 17,20-lyase activity prohibits the synthesis of androgens, which causes pseudohermaphroditism in males and sexual infantilism with primary hypogonadism in females.[7]

To date, more than 130 cases of 17OHD[7] and nearly 50 different mutations[8] in CYP17 have been reported, although they are more prevalent in certain ethnic groups, particularly in Brazilians and

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Japanese.[8,9] Here, we describe the clinical, hormonal and molecular genetic characteristics of a Taiwanese patient with 17OHD.

Case Report

This 15-year-old patient was an apparently normal female born to non-consanguineous parents. She weighed 3 kg when she was uneventfully delivered at full term, and had achieved normal developmental milestones. She had a history of hypertension, found incidentally during school screening 2 years previously, which did not respond to treatment with antihypertensive agent. There was no family history of chronic illness, including hypertension. The father and mother were 168 cm and 164 cm tall, respectively, and had normal pubertal and reproductive histories. She had an older sister with normal female phenotype and secondary sexual development with regular menstruation. The patient sought medical attention for sexual infantilism and uncontrollable hypertension. Meanwhile, she was depressed and suicidal as a result of her symptoms.

On physical examination, she had normal female external genitalia with a normal hymen. Breast and pubic hair development were Tanner stage I. She was 161 cm tall and weighed 48 kg. Her blood pressure was 163/81 mmHg at the first visit. Laboratory evaluation (Table) revealed hypokalemia (2.8 mmol/L) without alkalosis. Plasma 17-hydroxyprogesterone (0.39 mIU/mL; normal range, 0.49–2.3 mIU/mL) and cortisol (2.92 μg/dL; normal range, A.M.: 5–25 μg/dL, P.M.: half of A.M.) were decreased, and progesterone (1.7 ng/mL; normal range, < 0.6 ng/mL) was increased. Plasma ACTH (210 pg/mL; normal range, ND–46 pg/mL) was markedly elevated. Plasma renin activity was normal, but aldosterone level (400 pg/dL; normal range, 37.5–240 pg/dL) was high. Follicle stimulating hormone (70.2 mIU/mL) and luteinizing hormone (30.9 mIU/mL) were elevated and at adult castrate levels. Testosterone and estradiol levels were undetectable. Pelvic ultrasonogram revealed neither uterus nor ovaries, and testes were undetectable. Karyotype analysis was 46,XY. Bone age was 8.5 years for males and adrenal magnetic resonance imaging showed no abnormal findings.

In order to identify genetic mutations, polymerase chain reaction (PCR) amplification and

Table. Laboratory data before and after glucocorticoid replacement

Variable	Normal range	Months of treatment				
		0	1	2	6	7
ACTH	ND–46 pg/mL	210	16	–	77.1	–
Aldosterone	37.5–240 pg/dL	400	136	137	264	233
Renin	3.6–63.7 pg/dL (standing)	16.2	5.92	19.16	6.94	–
Cortisol	A.M.: 5–25 μg/dL P.M.: half of A.M.	2.92	–	–	–	–
17-OH PGTR	0.49–2.3 mIU/mL	0.39	–	–	–	–
Progesterone	M < 0.6 ng/mL	–	1.7	–	4.2	–
FSH	M: 1.5–14 mIU/mL	70.2	–	–	–	–
LH	M: 1.4–7.7 mIU/mL	30.9	–	–	–	–
Estradiol	M < 56 pg/mL	< 20	–	–	–	–
Testosterone	M: 2.7–17.3 ng/mL (20–40 yr)	< 0.2	–	–	–	–
Sodium	137–153 mmol/L	146	142	140	142	–
Potassium	3.5–5.3 mmol/L	2.8	3.4	3.8	–	3.5
pH/HCO_3	–	–	7.39/23.5	–	–	–

ACTH = adrenocorticotropic hormone; 17-OH PGTR = 17-hydroxyprogesterone; FSH = follicle stimulating hormone; LH = luteinizing hormone; M = male.

sequencing were performed after genomic DNA was extracted from peripheral blood. Exons 1–8 of the CYP17 gene were individually amplified by PCR with AmpliTaq Gold (Applied Biosystems, Foster City, CA, USA) as described previously.[10] Two different mutations were identified, including a point mutation S106P in exon 2 and a 9-bp (GACTCTTTC) deletion from nucleotide position 1519 in exon 8 of P450c17 (Figure). These results confirmed the diagnosis of 17OHD.

After the first month of treatment with dexamethasone (1 mg/day), systolic blood pressure was reduced from 161 mmHg to 139 mmHg, and potassium (3.4 mmol/dL), aldosterone (136 pg/mL) and ACTH (16 pg/mL) returned to within normal limits. Nevertheless, the patient was very concerned about the side effect of body weight gain with glucocorticoid therapy, so the dose was tapered (0.5 mg/day) from the second month of treatment. Potassium and aldosterone levels remained within normal levels but hypertension rebounded. Therefore, spironolactone (25 mg, QD) was added to the regimen from the third month. Systolic blood pressure decreased to 130–140 mmHg in the following months. During treatment, plasma ACTH and aldosterone were elevated (77.1 pg/mL and 264 pg/mL, respectively) due to poor drug compliance (Table). Estrogen replacement therapy to induce pubertal development was started soon after the clinical diagnosis of 17OHD. Her initial predicted adult height (by the Bayley and Pinneau method) was 208.3 cm, and bone age was measured according to the Greulich-Pyle method. Therefore, sex hormone replacement was increased rapidly for the purpose of reducing the predicted adult height and final height. Her last predicted adult height was 176.5 cm after hormone replacement therapy for 9 months.

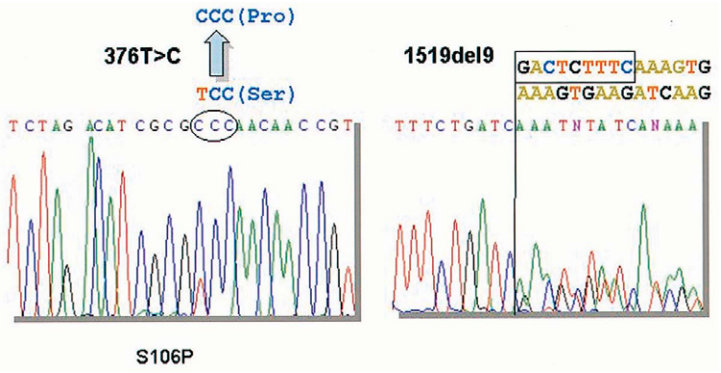

Figure. Direct genomic DNA sequence analysis of exon 2 and exon 8 of CYP17 in the index patient. The 9-bp (GACTCTTTC) deletion from nucleotide position 1519 of exon 8 and 376T>C (S106P) mutation of exon 2.

Discussion

The classical presentation of 17OHD is hypertension, hypokalemia and lack of secondary sexual development;[2] all of these features were found in our patient. Affected genetic males usually present with a complete female phenotypic appearance or, less often, with ambiguous external genitalia.[3,7] The magnitude of impaired masculinization in the male fetus correlates with enzymatic activity of the severity of the block in 17α-hydroxylation and the degree of the subsequent defect in fetal testosterone synthesis. Analysis of enzymatic activity has shown that more than 25% of normal activity is necessary for normal fetal masculinization of the external genitalia.[1,7] The clinical presentation of our patient was considered severe due to the completely female phenotype, although enzyme activity tests were not available in our country at the time of treatment.

In 17OHD, decreased cortisol secretion causes increased ACTH production, which results in overproduction of 17-deoxysteroids by the adrenal cortex, including DOC, corticosterone and 18-hydroxycorticosterone. However, data on 17-deoxysteroids were not obtained in our patient due to lack of availability of these tests in our country. Serum progesterone, which is one of the 17α-hydroxylase substrates and is a useful marker in the diagnosis of 17OHD,[11] was elevated in our patient. After ACTH stimulation test, the level of progesterone changed little, from 8.5 ng/mL to 8.7 ng/mL. The final diagnosis was confirmed by CYP17 genotyping.

Most patients with 17OHD have very low or subnormal production of aldosterone.[7,12] It has been suggested that the inhibition of aldosterone biosynthesis is mediated by the increased levels of DOC, which leads to suppression of the renin-

angiotensin system via an increased reabsorption of sodium and increased blood volume.[13] In contrast, serum aldosterone was elevated in this patient. Several other studies reported similar findings, especially in Japanese patients (16/20 cases).[7,12,14] Yamakita et al speculated that the more severe the deficiency of 17α-hydroxylase activity, the more active is the corticosterone methyl oxidase in fasciculata cells, resulting in greater production of aldosterone from corticosterone. Patients with severe deficiency of 17α-hydroxylase activity may fall into a broad category of glucocorticoid-remediable hyperaldosteronism.[9] 17OHD with glucocorticoid-remediable hyperaldosteronism, as well as elevated aldosterone levels that increased following ACTH stimulation and which responded to steroid replacement, has been reported.[14] Since our patient had no family history of hypertension, particularly in her parents, and neither her aldosterone level (from 317 pg/dL to 333 pg/dL) nor cortisol level (from 1.77 μg/dL to 2.59 μg/dL) were significantly responsive after 1-hour ACTH stimulation test, glucocorticoid-remediable aldosteronism was considered unlikely.

The renin-angiotensin-aldosterone axis is independent from the hypothalamus-pituitary-adrenal axis, and its regulation and interactions are very complicated. Therefore, the mechanism of low normal renin level in this case remains to be clarified.

Usually, hypertension resolves with glucocorticoid therapy,[15] but it may persist if the diagnosis is delayed.[16] Mineralocorticoid antagonists such as spironolactone or potassium canrenoate can be added to the regimen to achieve better control of blood pressure.[16] The addition of a calcium channel blocker to the regimen is usually effective if hypertension persists despite adequate blockade of mineralocorticoid production and action.[12,16]

Female sex assignment was continued in this chromosomally male patient due to established psychosexual development and identity. Estrogen replacement therapy was given for induction of female secondary sex characteristics. This therapy may also reduce final height.[17]

Prophylactic gonadectomy should be performed in genetic males with 17OHD because of the risk of malignant change. The testes may be intra-abdominal, in the inguinal canal, or in the labioscrotal folds.[1] As this patient was depressed and suicidal due to lack of sexual development, removal of gonads was postponed.

Nearly 50 different mutations in CYP17[8] have been reported since 1988.[18] Most of the mutations appear to be random, except for one reported in Canadian Mennonite descendants of Dutch Frieslanders.[7] In our patient, the compound heterozygous mutations, including a 9-bp (GACTCTTTC) deletion in exon 8 and S106P mutation in exon 2, were identified as inherited from the father and mother, respectively. Both of these mutations have been previously described in two unrelated Guamanian patients and a patient from Thailand, as well as in two siblings from China.[19–21]

In conclusion, 17OHD is a rare condition which has not been previously reported in Taiwan. It should be suspected in patients with hypokalemic hypertension and lack of secondary sexual development so that appropriate therapy can be implemented.

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